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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/653,924	09/01/2000	David A. Horwitz	A-67689-3/RFT/RMS/RMK	7255

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	13

DATE MAILED: 10/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/653,924	HORWITZ, DAVID A.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8,10-17 and 29-40* is/are pending in the application.

4a) Of the above claim(s) *5, 7-8,14, 16-18,34-36 and 38-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6,10-13,15,29-33 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 2-8,10-17 and 29-40 are pending.

2. Applicant's election without traverse of Group II, claims 2-8 and 10-17 in Paper No. 10 is acknowledged.

Applicant elected a suppressive inducing composition comprising a mixture of TGF-β and IL-2, PBMC enriched for CD3+CD4-CD8- cells and the T cell activator is anti-CD3 as the species. Claims 2-4, 6, 10, 12-13, 15, 29-33, and 37 read on the elected species.

Upon reconsideration, Examiner has extended the search to cover the suppressive inducing composition TGF-β in claim 11.

3. Claims 5, 7-8, 14, 16-17, 34-36 and 38-40 (non-elected species of the elected Group II) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 2-4, 6, 10-13, 15, 29-33 and 37 are under examination as they read on a method for treating donor cells to ameliorate grafte versus host disease in recipient patient, comprising PBMC enriched for CD3+CD4-CD8-, treating said cells with TGF-β or a TGFβ and IL-2 and the T cell activator is anti-CD3.

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. The disclosure is objected to because the title of Example 1, in page 21, line 15, is illegible. Correction is required.

7. The specification on page 1 should be amended to reflect the status of 09/261,890 and the relationship between 09/261,890 and the instant application.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 2-4, 6, 10-13, 15, 29-33 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a donor cells *ex vivo* to ameliorate graft versus host disease in a recipient patient comprising (a) removing peripheral blood mononuclear cells (PBMC) from a donor, (b) selectively enriching said PBMC for CD3+CD4-CD8- cells, (c) treating said cells with TGF-β oρ TGF-β and IL-2 suppressive-inducing composition to induce T cell tolerance or generate suppressor cells, and (d) introducing treated said cells to said patient; the method further comprises further treating the donor cell with anti-CD3 T cell activator and adding treated cells to donor stem cells prior to introduction into said patient, does not reasonably provide enablement for a method for treating donor cells to ameliorate graft versus host disease in recipient comprising treating **any PBMC** treated with **any suppressive-inducing composition** to induce T cell tolerance or generate suppressor cells in claims 2 and 10, wherein treating said donor cells with **any T cell activator** in claims 4 and 13; or a method for treating donor cells to ameliorate graft versus host disease in a recipient patient comprising **any suppressive-inducing composition** to generate suppressor cells in claim 32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

The specification discloses only a method for inhibiting GVHD by treating donor CD8+ cells from donor A and irradiated T cell- depleted mononuclear cells from donor B ex vivo with TGF-β however, the addition of IL-2 was not needed to demonstrate that TGF-β alone induces CD+T cells to suppress antibody production as well as to suppress cell-mediated immune responses (see page 22 in particular).

Besides TGF-β, IL-2, IL-4, IL-10, IL-15, Con A, anti-CD3, anti-CD28, SEB, anti-CD2, CD4+ cells, CD8+ cells or CD3+CD4-CD8-, the specification fails to provide any guidance as to how to make and how to use any "suppressive-inducing composition", any "PBMC" and any "T cell activator".

Other than the specific suppressive-inducing composition, T cell activators and PBMC mentioned above for a method for treating donor cells *ex vivo* to ameliorate graft versus host disease, Applicant has not provided sufficient biochemical information that distinctly identifies such "compositions" and "activators". While any "suppressive-inducing composition" may have some notion of the activity of the "inhibitory agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such compositions, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any cytokine, any antibody and mitogen that can be used to treat donor cells to ameliorate graft versus host disease.

The current state of the art in cytokines and mitogens therapeutics and the predictability of treatment efficacy is complicated. For example, Mysliwietz *et al* (IDS reference No. 93) teach ex vivo treatment of donor cells with a regulatory composition such as rat IgG2b anti-mouse CD3 MoAb (17A2) fails to induce T cell tolerance and suppress graft rejection such as GVHD (see abstract in particular). Therefore, one skilled in the art at the time of the invention would not be able to predict which compositions such as cytokines will elicit a reaction. Consequently the skilled artisan would not know how to use the instant invention as broadly claimed. While experimental testing techniques using PBMC cells suppressive-inducing compositions and T cell activator are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 2-4, 6, 10-13, 15, 29-33 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of for a method for treating a donor cells *ex vivo* to ameliorate graft versus host disease in a recipient patient comprising (a) removing peripheral blood mononuclear cells (PBMC) from a donor, (b) selectively enriching said PBMC for CD3+CD4-CD8- cells, (c) treating said cells with TGF-β or TGF-β and IL-2 suppressive-inducing composition to induce T cell tolerance or generate suppressor cells, and (d) introducing treated said cells to said patient; the method further comprises further

treating the donor cell with anti-CD3 T cell activator and adding treated cells to donor stem cells prior to introduction into said patient.

Applicant is not in possession of a method for treating donor cells to ameliorate graft versus host disease in recipient comprising treating any PBMC with any suppressive-inducing composition to induce T cell tolerance or generate suppressor cells in claims 2 and 10, wherein treating said donor cells with any T cell activator in claims 4 and 13; or a method for treating donor cells to ameliorate graft versus host disease in a recipient patient comprising any suppressive-inducing composition to generate suppressor cells in claim 32.

Applicant has disclosed TGF-β, IL-2, IL-4, IL-10, IL 15, Con A, anti-CD3, anti-CD28, SEB, anti-CD2, CD4+ cells, CD8+ cells or CD3+CD4-CD8- cells; therefore, the skilled artisan cannot envision all the contemplated suppressive-inducing composition and T-cell activator possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 2-3, 6, 10-12, 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-4 of U.S. Patent No. 6,447,765. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims 1, 3-4 teach a method of treating a donor cells to ameliorate graft versus host disease in a recipient patient comprising (a) removing peripheral blood mononuclear cells (PBMC) from a donor; (b) treating said cells with a suppressive composition comprising TGF-β for a time sufficient to induce T cell tolerance; and (c) administering said cells to said patient in patented claim 1, wherein said suppressive composition further comprises IL-2 in patented claim 4, and the method further comprises adding said cells to donor stem cells prior to administering to said patient in patented claim 3. The generation of suppressor cells in instant claims 10, 12 and 15 is considered inherent properties of the claimed method, because both the reference teachings and the claimed invention involved the same method of treating donor cells to ameliorate graft versus host disease in a recipient patient which comprises administration of same product to the same recipient patient.

13. Claims 4, 13, 33 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-4 of U.S. Patent No. 6,447,765 in view of U.S. Patent No. 6,406,696.

Claims 1, 3-4 of the ``765 patent have been discussed, supra.

The claimed invention differs from the reference claims 1, 3-4 recitations only by the recitation the method further comprising treating said donor cells with a T cell activator in claims 4 and 13; wherein said T cell activator is anti-CD3 in claims 33 and 37.

The `696 patent teaches immunopotentiating agents include monoclonal antibodies, such as anti-CD3 which activate T cells (see abstract in particular). Moreover, the `696 patent teaches the

ability of anti-CD3 to abrogate graft versus host disease (GVHD) in a murine model wherein the anti-CD3 mAb treatment also enhanced bone marrow engraftment (column 12, lines 42-46 in particular) and the circulating anti-CD3 antibody would modulate TcR from host T cells and thereby inhibit HVD reactions (column 18, lines 50-54 in particular). Furthermore, monoclonal antibodies (mAb) to T lymphocyte antigens have been used to suppress immune responses in vivo and in vitro by blocking T cell receptor-mediated antigen recognition, a property exploited clinically to prevent and reverse organ transplant rejection (column 14, lines 62-65 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to further activate the recipient T cells with anti-CD3 antibody taught by the `696 patent in the method of treating donor cells to a meliorate graft versus host disease taught by the `765 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such immunopotentiating antibodies suppress immune responses in vivo and in vitro by blocking T cell receptor-mediated antigen recognition, a property exploited clinically to prevent and reverse organ transplant rejection as taught by the `696 patent.

14. Claims 29-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-4 of U.S. Patent No. 6,447,765 in view of Sykes *et al* (Cell Immunol. 1990 Sep;129(2):478-93).

Claims 1, 3-4 of the ``765 patent have been discussed, supra.

The claimed invention differs from the reference claims 1, 3-4 recitations only by the recitation that PBMC are enriched for CD3+CD4-CD8- cells.

Sykes *et al* teach that enriching and then propagating natural suppressor cells derived from T cell-depleted cells *in vitro* can enhance anti-GVHD effect by adoptive transfer in vivo. Using IL-2 to produce two cell lines of BMC depleted of Mac1-positive cells and of Mac1-positive plus Thy1-positive cells, these cells express CD3 but not CD4 or CD8 (page 490, under Discussion in particular). These cell lines demonstrated suppressive activity in vitro, cytolytic activity against a broad range of natural killer (NK)-sensitive and NK-resistant targets, and a novel cell surface phenotype, with characteristics of both alpha beta-TcR-bearing T cells and of NK cells. Sykes *et al* further teach that natural suppressor (NS) cells derived from T cell-depleted (TCD) syngeneic marrow can protect against GVHD while permitting alloengraftment (see abstract and page 478 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to enrich PBMC for CD+CD4-CD8- cells taught by Sykes *et al* reference in the method of treating donor cells to a meliorate graft versus host disease taught by the `765 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such enriched cells can be protective against GVHD while permitting alloengraftment as taught by Sykes *et al.*

15. No claim is allowed.

16. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

17. **1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

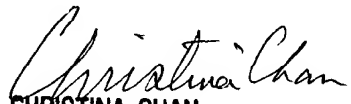
Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
September 30, 2002



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